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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,728	07/03/2001	John F. Wironen	RTI-133	8170

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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/897,728	WIRONEN ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 31* is/are rejected.

7)☒ Claim(s) *4,14 and 19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/25/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' elections with traverse of Group I (claims 1-23) and species (allograft and the combination of two factors: bone morphogenic proteins and tissue growth factors, filed 1/23/04, are acknowledged. Amended claims 1, 11, 16, 23, and 31 and cancelled claims 24-30 are acknowledged. Claim 31 has been added to Group I due to claim amendments. Upon further consideration by the Examiner, the specie election requirement for osteoinductive/osteogenic factors has been removed.

Applicants' traversal is on the grounds of rejoining claim 31 to Group I and that there should be no species requirement regarding bone implant materials.

The applicants' request to combine claim 31 to Group I has been granted. The Applicants' request to withdraw the bone implant material species election was found unpersuasive because of the following reasons:

The species requirement of bone material is merely to assist the Examiner in narrowing down the initial search of the claims. If this species is found to be allowable then species requirement will be withdrawn. Although these species may not be considered to be mutually exclusive, they also are not necessarily coextensive in nature. For example, allograft has different features from autograft and xenograft. Also, while an allograft may comprise cortical bone, cancellous bone, or combinations thereof, an allograft may not contain all of these features and thus are not necessarily coextensive in nature. Therefore, these species are considered to be

patentably distinct with divergent subject matter, so the species election will be maintained at the present time, regardless of its importance or lack thereof in the method, as stated by Applicants.

The requirements are still deemed proper and are therefore made FINAL.

The information disclosure statement, filed 9/25/03, fails to comply with the provisions of 37 CFR 1.97, 1.98, and MPEP § 609, because the international search report (C1) is not a publicly published document. This search report has been looked at the Examiner but not formally acknowledged as being considered on the merits for the reason stated above.

Claims herein under examination are 1-23 and 31.

Claim Objections

Claims 4, 14, and 19 are objected to because of the following minor informalities: In claim 4, "dimineralizing" on line 2 is misspelled. In claim 14, a comma is missing after "TGF-β" on line 3. In claim 19, "pictogram" is misspelled on line 2. Appropriate correction is requested.

Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 1 (line 9) and 23 (line 7) recite the phrase "use of *complex* biological living materials" which is vague and indefinite. One of skill in the art would argue that all biological living material is complex, be it a gene or a tissue. Therefore, it is unclear what are the metes and bounds of the term "complex" in this phrase. Clarification of this issue via clearer claim wording is requested. Claims 2-22 and 31 are also rejected due to their direct or indirect dependency from claim 1.

Claim 1 (line 12) and 23 (line 10) recite the term "corresponding" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered to be corresponding. Clarification of the metes and bounds of the claims via clearer claim wording is requested. Claims 2-22 and 31 are also rejected due to their direct or indirect dependency from claim 1.

Claim 1 (line 12) and 23 (line 10) recite the phrase "similar value" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered to be similar. Is this similar value also an osteogenic potential value? Clarification of the metes and bounds of the claims via clearer claim wording is requested. Claims 2-22 and 31 are also rejected due to their direct or indirect dependency from claim 1.

Claim 4 (line 2) recite the phrase "substantially demineralized" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered to be substantially demineralized. Clarification of the metes and bounds of the claim

via clearer claim wording is requested. Claims 5-11 are also rejected due to their direct or indirect dependency from claim 4.

Claims 10 (line 1) and 11 (line 2) recite the term "low" which is vague and indefinite. It is unclear what criteria or threshold applicants require for the molecular weight to be considered low. Clarification of this issue via clearer claim wording is requested.

Claim 13 recites the limitation "said at least one osteoinductive factor" on lines 1 and 2. There is insufficient antecedent basis for this limitation in this claim or claim 1 from which it is dependent.

Claim 18 (line 3) recite the phrase "under conditions" which is vague and indefinite. It is unclear what parameters and to what degree these parameters must be met to be considered to be under conditions to allow for specific binding. Clarification of the metes and bounds of the claim via clearer claim wording is requested.

Claim 19 recites the limitation "said osteoinductive factors" on lines 1 and 2. There is insufficient antecedent basis for this limitation in this claim or claim 1 from which it is dependent.

Claims Rejected Under 35 U.S.C. § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF SCOPE OF ENABLEMENT

Claims 1, 12-23, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for bone implants, does not reasonably provide enablement for implant materials other than those that are listed in instant claims 2 and 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses a method for quantifying the osteoinductive capacity of bone implants (page 10, lines 3-4); however, it does not provide enablement for implant material practice beyond the materials listed in instant claims 2 and 3. Claim 1, for example, seems to include any implant material as a source of osteogenic factors. On page 11, last paragraph, of the specification, the implant is said to "imply any material which is non-toxic and compatible with

human or non-human vertebrate tissues, and which is useful in correction, repair, augmentation, or alteration of bone structures in the humans or non-human recipient of the implant." Working examples do provide enablement for the bone implant materials, such as autograft, allograft, xenograft, cortical bone, cancellous bone, and combinations thereof (as stated in instant claim 3), but not for implant materials beyond this disclosure. Because claims 1, 12-23, and 31 encompass other implant materials that were not adequately disclosed in the specification, claims, and drawings, as originally filed, one of skill in the art would not know how to make and use the invention beyond using the bone implant materials discussed above. Therefore, this is a lack of scope of enablement rejection.

Claim Rejections – 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 19-20, 22-23, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (Journal of Periodontology, 1997 Nov; Vol. 68(11), pages 1076-1084).

Zhang et al. disclose an in vitro method for quantifying the osteoinductive potential of demineralized bone matrix (a collection of like implant material) from cadaverous humans before clinical (human) use (allograft) (title; abstract; page 1077, col. 2, second paragraph), as

stated in instant claims 1 and 23. Zhang et al. disclose exposing ground bone (implant material) to dilute hydrochloric acid, a demineralization process to dissolve the bone material (page 1077, col. 1, last paragraph to col. 2, first paragraph) as stated in instant claims 4 and 5. Instant claim 4 states that the demineralizing bone implant material comprises reducing calcium concentration which is optional, as stated in instant claim 4, and therefore not a definite requirement of the claim limitation. Zhang et al. disclose the bone matrices being separated into particles according to size ranges with sieves (page 1077, col. 1, last paragraph). Zhang et al. disclose combining bone cells with EDTA and trypsin (enzyme) (page 1078, col. 1, third paragraph) which represents dissolving the bone implant matrix with an enzyme, as stated in instant claim 6. Trypsin is utilized for cell detachment and does not destroy osteoinductive factors, as stated in instant claim 6. Zhang et al. disclose quantifying the concentration of alkaline phosphatase (ALP) (implant material releasant of osteogenic factor) via a protein assay using milligram quantities (page 1078, col. 1, last paragraph to col. 2, first paragraph) as stated in instant claims 1, 19, and 23. Zhang et al. disclose mesenchymal cell induction process (morphogenic) is frequently monitored by changes in ALP activity of cells being studied (page 1081, col. 1, second paragraph). Zhang et al. disclose changes in ALP level with time were studied to assess effects of DBM on human periosteal cell induction (page 1081, col. 1, second paragraph). Zhang et al. disclose noting changes in ALP concentration with a similar value on a curve to determine osteogenic potential of implant material (Figures 6 and 7), as stated in instant claims 1 and 23. Zhang et al. disclose osteoinductivity of demineralized bone matrix is due to bone morphogenetic proteins (BMPs) and other noncollagenous proteins in the matrix (page 1077, col. 1, third paragraph). Zhang et al. disclose proliferation effects of demineralized bone matrix were

studied to assess potential mitogenic effects (page 1080, col. 2, second paragraph). Zhang et al. disclose a correlation graph between in vitro of ALP activity (concentration) and percent calcium (probability to generate bone in vivo) (Figure 8), as stated in instant claim 20. Zhang et al. disclose using periosteal cells which are presumed to be responsive to BMPs actions, differentiating into osteoblast cells (Figure 8 and page 1083, col. 1, third and fourth paragraphs), as stated in instant claim 22. Zhang et al. disclose the in vitro assay may be a good substitute for the in vivo assay in assessing osteoinductive potential of demineralized bone matrix and reduce animal use via quality assessment (select bone material) for clinical application (to be implanted into patient) (page 1083, col. 1, last paragraph to col. 2, first paragraph), as stated in instant claim 31.

Thus, Zhang et al. anticipate the limitations in claims 1-6, 19-20, 22-23, and 31.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

Ardin H. Marschel 4/5/04
ARDIN H. MARSCHEL
PRIMARY EXAMINER

March 31, 2004